

Resolution without discontinuation: heart failure during clozapine treatment

Eromona Whiskey^{ID}, Shirley Yuen, Emma Khosla, Susan Piper, David O'Flynn and David Taylor^{ID}

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Abstract: Clozapine is an atypical antipsychotic recommended for patients with treatment-resistant schizophrenia whose illness has not responded adequately to treatment despite the sequential use of at least two different antipsychotic drugs at therapeutic doses. Unfortunately, clozapine is frequently discontinued due to both real and perceived serious, and potentially life-threatening, adverse effects, contributing to the underutilisation of the most effective treatment in refractory psychotic disorders. Here, we present the case of a 51-year-old man with treatment-resistant schizoaffective disorder, who was admitted to a locked rehabilitation unit for a clozapine rechallenge. Within 6 months after the clozapine rechallenge, he was diagnosed with heart failure likely secondary to his antipsychotic treatment. Clozapine-induced heart failure usually prompts immediate cessation of treatment. However, in this case, clozapine was continued with cardiology consultation. Ramipril and bisoprolol were initiated and the patient's cardiac condition progressively improved over time. Clozapine-induced heart failure is a serious cardiovascular complication of treatment, usually resulting in discontinuation of treatment. Although there are cases of successful rechallenge, temporary cessation of treatment can lead to severe psychotic exacerbation and non-engagement with cardiac specialists. More evidence is required for continued use of clozapine in a patient with clozapine-induced cardiac complications.

Keywords: cardiomyopathy, clozapine, heart failure, myocarditis, rechallenge

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Background

Clozapine is an atypical antipsychotic recommended for patients with treatment-resistant schizophrenia whose illness has not responded adequately to treatment despite the sequential use of at least two different antipsychotic drugs at therapeutic doses. Clozapine has demonstrated superior efficacy in refractory schizophrenia compared with other antipsychotics.^{1,2} Unfortunately, it is grossly underutilised and discontinued prematurely for a variety of reasons – including the need for mandatory regular blood monitoring,^{3,4} clinicians' lack of experience with the drug and negative attitudes towards it,⁵ and concerns regarding the risk of potentially fatal adverse

effects such as agranulocytosis, myocarditis and severe gastrointestinal disorders.^{6–8}

Case presentation

The patient is a 51-year-old man of Somali origin with a diagnosis of treatment resistant schizoaffective disorder, who first came to the UK in 1990. He was referred to psychiatric services in 2001 at the age of 31. For the 8-year period following this, he had a number of psychiatric admissions due to frequent relapses in his mental state. It was not until 2010, when he was started on clozapine together with lithium during an admission, that he experienced good clinical response.

Correspondence to:
Eromona Whiskey
Pharmacy department,
South London and
Maudsley NHS Foundation
Trust, Denmark Hill,
London, UK
Institute of Pharmaceutical
Sciences, Kings College
London, London, UK
Eromona.Whiskey@slam.nhs.uk

Shirley Yuen
Pharmacy department,
South London and
Maudsley NHS Foundation
Trust, London, UK

Emma Khosla
David O'Flynn
Department of
Rehabilitation Psychiatry,
South London and
Maudsley NHS Foundation
Trust, London, UK

Susan Piper
Department of Cardiology,
Kings College Hospital,
London, UK

David Taylor
Pharmacy department,
South London and
Maudsley NHS Foundation
Trust, London, UK
Institute of Pharmaceutical
Sciences, Kings College
London, London, UK



Unfortunately, later in the year 2010, the patient travelled abroad and ran out of medication, resulting in relapse. He was admitted to hospital under Section 3 of the Mental Health Act (MHA) upon return to Britain.⁹ This section allows for a person to be admitted to hospital for treatment if their mental disorder is of a nature and/or degree that requires treatment in hospital. In addition, it must be necessary for their health, their safety or for the protection of other people that they receive treatment in hospital. He has been hospitalised almost continuously since then. Up until 2017, when he was referred to our unit, he had been managed in various psychiatric in-patient settings. He was trialled on clozapine on two further occasions but discontinued each time in the context of poor compliance with oral treatment and blood monitoring. Treatment with clozapine showed good response and relative stability in his mental state, as compared with rapid and severe deterioration seen with discontinuation. When unwell and severely psychotic he presented as highly distressed, with high risk towards himself in the form of suicide attempts and self-neglect, and towards others through verbal threats and episodes of violence in response to his psychotic experiences.

During the brief periods when he received clozapine treatment (in total, less than 12 months), he developed cardiac symptoms. In 2012, he had episodes of tachycardia and chest pain and a partial right bundle branch block (RBBB) was noted on his electrocardiogram (ECG). Due to non-attendance at cardiology appointments, he was discharged from cardiology follow up. In 2015, he had persistent tachycardia on clozapine and attended accident and emergency (A&E) after he developed palpitations, chest pain and shortness of breath, with evidence of a soft systolic murmur on examination. In 2016, RBBB was again noted on an ECG, but his consistent refusal to attend cardiology investigations and clinics hampered any further assessment of this. Cardiology advice given at the time was to limit clozapine dose to a maximum of 150 mg daily in the absence of further investigation, preventing the attainment of therapeutic levels. He discontinued treatment shortly after.

In the intervening periods of clozapine discontinuation, multiple other treatment approaches were trialled with inadequate response. The medications trialled included zuclopentixol decanoate depot, risperidone long-acting injection, haloperidol decanoate depot, aripiprazole depot and

eventually oral olanzapine before referral and transfer in June 2017 to our unit, a locked rehabilitation ward, with an aim to re-challenge with clozapine alongside investigation of his cardiac function. At the time of transfer, he was taking olanzapine 20 mg, semi-sodium valproate 1.5 g and regular benzodiazepine, clonazepam, for agitation. Other medications prescribed included vitamin D, aspirin and lansoprazole. His medical history at this point included an old non-healed fractured left humerus, clozapine-induced constipation, and a fully treated pulmonary tuberculosis (TB).

On transfer in June 2017, RBBB on ECG and a systolic murmur on examination were present, though, in his severely unstable mental state, he continued to refuse cardiology investigations and appointments. Cardiology advice was sought, which did not object to clozapine rechallenge, but advised to monitor ECG and troponins during treatment.

The patient was eventually re-commenced on clozapine in January 2018, and titrated to 300 mg daily using an oral/intramuscular titration regimen. In the third week of clozapine titration at a dose of 350 mg daily, he experienced persistent cough and was feeling generally unwell. Bloods showed normal troponin and a mildly raised C-reactive protein (CRP). ECG showed T-wave inversion, borderline prolonged PR interval and a QTc of 440 msec. He was treated for suspected pneumonia with antibiotics and clozapine treatment continued. Following considerable improvement in mental state, the team were able to take him for an echocardiography in June 2018, which demonstrated moderate-to-severely reduced left ventricular function, with an ejection fraction of 37%. He was given a diagnosis of left ventricular heart failure by cardiologists at King's College Hospital, and commenced on ramipril and bisoprolol. At the time of this diagnosis, the decision was made with cardiology to maintain treatment with clozapine at a dose of 300 mg daily as it had been highly beneficial to his mental state.

Further advice was sought in October 2018 regarding a potential increase in clozapine as the patient remained unwell. His clozapine level was 0.24 mg/l, which is below the recommended range of 0.35–0.5 mg/l according to the Maudsley prescribing guidelines.¹⁰ However, cardiology advised against dose increases without an improvement in cardiac function. Both ramipril and

bisoprolol were gradually titrated upwards to 10 mg daily with close monitoring of blood pressure, heart rate and renal function, particularly in the context of co-prescription with lithium. Eplerenone 25 mg was added to heart failure treatment in November 2018; however, this was discontinued following worsening renal function and an increase in lithium levels.

A repeat echocardiogram in November 2018 showed that the patient's cardiac function had improved with treatment using ramipril and bisoprolol, and his left ventricular function was within normal limits, with an ejection fraction of 56%. The subsequent advice from the cardiology team was that, in light of the improved ejection fraction, it would be safe to continue clozapine and that further increases could be done alongside ECG and troponin measurements.

Discussion

Our unit is a 16-bedded specialist rehabilitation facility with expertise in treatment of patients with refractory psychotic disorders and experience of clozapine rechallenges working with various medical teams including cardiologists, haematologists and neurologists.

Cardiotoxicity is one the limiting factors to greater clinical utility of clozapine. At the first signs of cardiac toxicity, clozapine is usually discontinued. This is because, unlike haematological monitoring for neutropenia and agranulocytosis, there is no widely accepted and recognised guideline for cardiac monitoring of clozapine treatment. A clozapine myocarditis monitoring protocol recommends baseline echocardiography with weekly assessment of troponin and CRP.¹¹ Unfortunately, this rarely happens in routine clinical practice and is not recommended by the manufacturer's summary of product characteristics (SPC). In addition, compliance with physical health monitoring such as ECG and blood monitoring during periods of acute psychiatric exacerbation is often poor, and pragmatic approaches in assessing risk benefit is frequently the norm.

It was recognised that this patient is at an increased risk of clozapine cardiac effects. However, a proper cardiology assessment was not possible before clozapine rechallenge. The decision for rechallenge was thus based on a pragmatic evaluation of the risk. Indeed, clozapine initiation was facilitated only using intramuscular clozapine.¹²

Unlicensed clozapine injection is manufactured by Apothek A15® (formerly Brocacef®) in the Netherlands and was approved by the Drugs and Therapeutics Committee of the South London and Maudsley (SLaM) National Health Service (NHS) Foundation Trust in 2016.

Cardiovascular adverse effects associated with clozapine can be conceptualised as early occurring or late occurring, with the early occurring symptoms potentially giving rise to the late occurring.¹³ Also, subclinical cardiotoxicity has also been reported with clozapine and it has been suggested that improved outcomes can be achieved by earlier recognition of potential cardiotoxic effects well before clinical manifestations and cardiac function impairments associated with overt myocarditis and cardiomyopathy have developed.¹⁴ It is therefore possible that our patient may have experienced subclinical cardiotoxicity during clozapine titration, subsequently manifesting as left ventricular heart failure.

At the time of diagnosis of left ventricular heart failure following echocardiography, our patient was asymptomatic. In several fatal cases, no clinical symptoms suggestive of cardiac function impairment were noted before death.⁷ However, during previous clozapine trials, he had developed palpitations, chest pain, and shortness of breath with evidence of a systolic murmur on examination. Many patients that develop myocarditis, especially those with mild symptoms, go undiagnosed.¹⁵

Clozapine-related cardiomyopathy or heart failure usually elicits prompt discontinuation. Several reports noted that there was an improvement in cardiac function on echocardiogram after cessation of clozapine. A systematic review of clozapine induced cardiomyopathy demonstrated that, after cessation of clozapine and initiation of guideline based heart failure treatment, patients with an ejection fraction of <25% have a poor prognosis¹⁶; those with an ejection fraction of 25–40% generally show significant improvement and those with an ejection fraction of >40% usually show near complete recovery of cardiac function at 6 months. A recent review, however, notes that cessation of clozapine, whilst sometimes necessary, is not always mandatory.¹³ The authors suggest that well-established medical therapies for left ventricular dysfunction that can significantly improve cardiac function may facilitate continued therapy with clozapine, akin to practices seen in the cardio-oncology setting.

Rechallenge after clozapine cessation after myocarditis or cardiomyopathy have been reported with both successful and unsuccessful outcomes. Previous reports have demonstrated that beta-blockers and angiotensin converting enzyme (ACE) inhibitors may allow rechallenge in such patients.¹⁷ More recently, a case of continuation of clozapine after a diagnosis of cardiomyopathy was reported in a 42-year-old man with treatment-resistant schizophrenia by treating with ramipril and bisoprolol.¹⁸

In summary, the reintroduction and titration of clozapine to a therapeutic dose led to sufficient improvement in the patient's mental state that allowed for the assessment of his cardiac function, which showed a moderate-to-severe reduction in left ventricular function. Under consultation with cardiology, clozapine was continued alongside heart failure medications, with good improvement in left ventricular function observed.

Although he has had a marked improvement in mental state and functioning on his current treatment plan, the patient still remains disabled by his ongoing psychotic and affective symptoms, and also requires close monitoring of his blood pressure, renal function and lithium levels. The current plan is to continue adjustments in psychotropic medication with close physical health monitoring, and to liaise with cardiology for consideration of augmentation agents to further improve his mental state whilst also maintaining cardiac function. We are looking for him to step down to an open rehabilitation unit.

This case demonstrates that there is a real need for a multidisciplinary team of specialist cardiologists working with psychiatrists and pharmacists in preventing premature termination of clozapine treatment. In addition, there is an urgent need for evidence-based guidelines for cardiac monitoring of clozapine. A yellow card report of the reaction was filed with the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) in accordance with guidelines for submitting adverse events.¹⁹

Authors' contributions

SY and EK compiled the clinical information. DO, EW, EK and SP were directly involved in the treatment of the patient. EW drafted the manuscript. EW, DO and DT made substantial contribution in revising the manuscript critically and supplied important intellectual content. All authors read and approved the final manuscript.

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Not applicable.

ORCID iDs

Eromona Whiskey  <https://orcid.org/0000-0002-6146-0073>

David Taylor  <https://orcid.org/0000-0002-2557-1710>

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